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(54) Title: METHOD FOR TREATING CERVICAL CANCER

(57) Abstract: Use of Interleukin-20 for treating cervical cancer or cells infected with human papilloma virus . IL-20 can be administered alone or in conjunction with radiation or chemotherapeutic agents or surgical excision of the involved cells or lesions.

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METHOD FOR TREATING CERVICAL CANCER

BACKGROUND OF THE INVENTION

According to the American Cancer Society, 12,800 new cases of invasive cervical cancer would be diagnosed in the United States in 1999. During the same year, 4800 patients were expected to die of the disease. This represents approximately 1.8% of all cancer deaths in women and 18% of gynecological cancer deaths. However, for women aged 20 to 39 years of age, cervical cancer is the second leading cause of cancer deaths. Molecular and epidemiologic studies have demonstrated a strong relationship between human papillomavirus (HPV), cervical intraepithelial neoplasia, (CIN), and invasive carcinoma of the cervix. Thus, there is a need to develop new therapeutic entities for the treatment of human papillomavirus infection, cervical intraepithelial neoplasia and carcinoma of the cervix.

DESCRIPTION OF THE INVENTION

The present invention fills this need by administering interleukin-20 (IL-20) to a mammalian having cervical cancer. IL-20 can also be used to treat a human papillomavirus infection. The present invention also provides a method for inhibiting the growth of cervical cancer cells by bringing IL-20 into contact with said cancerous cervical cells. Interleukin-20 (formally called Zcyto10) can be produced according to the method described in International Patent Application No. PCT/US98/25228 filed on November 25 1998. The human IL-20 polypeptide is comprised of a sequence of 176 amino acids with the initial Met as shown in SEQ ID NO:1 and SEQ ID NO:2. It is believed that amino residues 1-24 are signal sequence, and the mature IL-20 polypeptide is represented by the amino acid sequence comprised of residues 25, a leucine, through amino acid residue 176, a glutamic acid residue, also defined by SEQ ID NO:12. Another embodiment of the present invention is defined by the sequences of SEQ ID NO: 3 and SEQ ID NO: 4. The polypeptide of SEQ ID NO: 4 is comprised of

151 amino acid residues wherein amino acids 1-24 comprise a signal sequence and the mature sequence is comprised of amino acid residues 25, a leucine, through amino acid 151 a glutamic acid, also defined by SEQ ID NO:13. Another active variant is comprised of amino acid residues 33, a cysteine, through amino acid residue 176 of SEQ ID NO:2. This variant is also defined by SEQ ID NO:26.

Mouse IL-20 is also a polypeptide comprised of 176 amino acid residues as defined by SEQ ID NOs: 18 and 19. Mouse IL-20 has a signal sequence extending from amino acid residue 1, a methionine, extending to and including amino acid residue 24, a glycine of SEQ ID NO:19. Thus, the mature mouse IL-20 extends from amino acid residue 25, a leucine, to and including amino acid residue 176 a leucine of SEQ ID NO:19, also defined by SEQ ID NO:20. Another active variant is believed to extend from amino acid 33, a cysteine, through amino acid 176, of SEQ ID NO:19. This variant is also defined by SEQ ID NO:25.

A variant of mouse IL-20 is defined by SEQ ID NOs: 33 and 34. This variant is 154 amino acid residues in length and has a signal sequence extending from amino acid residue 1, a methionine, to and including amino acid residue 24, a glycine, of SEQ ID NO:34. Thus, the mature sequence extends from amino acid residue 25, a leucine, to and including amino acid residue 154, a leucine, of SEQ ID NO:34. The mature sequence is also defined by SEQ ID NO:35.

Pathology of Cervical Cancer

Cervical dysplasia cells and cervical intraepithelial neoplasia (CIN) cells develop into invasive cervical cancer over a number of years. CIN grades I, II and III correspond to mild, moderate, and severe cervical dysplasia. CIN III, which includes severe dysplasia and carcinoma *in situ*, is unlikely to regress spontaneously and, if untreated, may eventually penetrate the basement membrane, becoming invasive carcinoma. Squamous cell carcinoma accounts for 80 to 85% of all cervical cancers; adenocarcinomas account for most of the rest. Invasive cervical cancer usually spreads by direct extension into surrounding tissues and the vagina or via the lymphatics to the pelvic and para-aortic lymph nodes drained by the cervix. Hematologic spread is possible.

Symptoms, Signs and Diagnosis of Cervical Cancer

CIN is usually asymptomatic and discovered because of an abnormal Pap smear. Patients with early-stage cervical cancer usually present with irregular vaginal bleeding, which is most often postcoital, but intermenstrual bleeding or menometrorrhagia may occur. Patients with larger cervical cancers or advanced-stage disease may present with foul-smelling vaginal discharge, abnormal vaginal bleeding, or pelvic pain. Obstructive uropathy, back pain, and leg swelling are manifestations of late-stage disease. Suspicious lesions, generally first detected by a Pap smear are biopsied. If clinical disease is invasive, staging is performed on the basis of the physical examination, with a metastatic survey including cystoscopy, sigmoidoscopy, IV pyelography, chest x-ray, and skeletal x-rays.

Treatment of Cervical Cancer with IL-20

Cervical cancer can be treated by administration of IL-20 to a female mammal, particularly a human female, afflicted with the disease. IL-20 can be administered intralesionally, or intramuscularly for localized disease. For metastatic disease, IL-20 can also be administered by intraperitoneal administration including intravenous administration. IL-20 can be administered alone or in conjunction with standard therapies such as surgery, radiation or other chemotherapeutic agents such as bleomycin, chlorambucil, epirubicin, 5-fluorouracil, ifosfamide, mitomycin, methotrexate, vincristine, cisplatin and vinblastine.

Use of Interleukin-20 to Treat Cells Infected with the Human Papillomavirus/Genital Warts

Cells infected with the human papillomavirus (HPV) can be treated with IL-20 to inhibit the proliferation of the virus. Anogenital warts caused by HPV type 6, 11, 16, 18, 31, 33 and 35 are transmitted sexually and have an incubation period of 1 to 6 months. Endocervical wart infections caused by type 16 or 18 have been implicated as a cause of cervical intraepithelial neoplasia and cervical cancer. HPV types 16 and 18 generally do no not cause external genital warts, which are usually caused by types 6 and 11.

Symptoms, Signs and Diagnosis

Genital warts usually appear as soft, moist, minute pink or gray polyps that enlarge, may become pedunculated, and are usually found in clusters. The surfaces resemble the surface of cauliflower. In men they occur most commonly on warm, moist surfaces in the subpreputial area, on the coronal sulcus, within the urethral meatus, and on the penile shaft. In women, the vulva, the vaginal wall, the cervix, and the perineum may become involved. They are particularly common in the perianal region and rectum in homosexual men. Growth rates vary, but pregnancy, immunosuppression, or maceration of the skin may accelerate both the growth of individual lesions and their spread. Genital warts usually can be identified by their appearance but must be differentiated from the flat-topped condyloma lata of secondary syphilis. Biopsies of atypical or persistent warts may be necessary to exclude carcinoma.

IL-20 can be administered directly into lesions containing cells infected with HPV alone or with standard therapies such as interferon alpha or interferon beta both of which are commercially available. Interferon alpha is available from Schering Corporation of Kenilworth, New Jersey and is called INTRON A®. Interferon beta is produced by Biogen of Cambridge, MA and is called AVONEX ®. IL-20 can also be administered with other standard therapies for treating HPV including antimitotics such as podophyllotoxin, podophyllin, or 5-fluorouracil; caustics such as trichloroacetic acid; or interferon inducers such as imiquimod.

The quantities of IL-20 for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medications administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in vivo* administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Methods for administration include, intravenous, peritoneal, intramuscular, or intralesional. Pharmaceutically acceptable carriers will include water, saline, buffers to name just a few. Dosage ranges would ordinarily be expected from 1μg to 1000μg per kilogram of body weight per day. However, the doses may be higher or lower as can be determined by a medical doctor with ordinary skill in the art. Excipients and stabilizers can possible be added. These include glycine, histidine, glutamate, aspartate, sugars, sucrose, trehalose, galactose sorbitol, arginine, D-and/or L0amino acids, sugar alcohols, lactose, maltose, threonine, lysine, methionine, isoleucine, a surface active agent such as TWEEN 80, TWEEN 20,

polyethylene glycol (PEG) (particularly those PEGs having molecular weights between 1000 and 35000 Da), cetyl alcohol, polyvinylpyrrolidone, polyvinyl alcohol, lanolin alcohol and sorbitan. A reducing agent may be included, such as cysteine, N-acetyl-cysteine, and thioglycerol. For a complete discussion of drug formulations and dosage ranges *see Remington's Pharmaceutical Sciences*,18th Ed., (Mack Publishing Co., Easton, Penn., 1996), and *Goodman and Gilman's: The Pharmacological Bases of Therapeutics*,9th Ed. (Pergamon Press 1996).

IL-20 can also me administered in conjunction with other treatments for cervical cancer such as radiation and chemotherapy. Examples of chemotherapeutic agents include bleomycin, chlorambucil, epirubicin, 5-fluorouracil, ifosfamide, mitomycin, methotrexate, vincristine, cisplatin and vinblastine.

Example

We tested IL-20 in a HeLa299 cytotoxicity assay to measure the ability of IL-20 to prevent cells from growing during normal growth conditions. We used MTT reagent (Promega, Madison, USA) as our detection and readout for this cell inhibition assay . Procedure of a cytoxicity assay:

Day 1- Plate cells out in complete growth media (with serum) at 5000cells/well in a 96well format and let them incubate overnight at 37degrees and 5% CO2.

Day 2- Dump off media and add a dose response of appropriate ligands in complete growth media (IL-20, zmda1, and MDA7 at 10, 100, and 1000 ng/ml.), along with a positive control retinoic acid (100uM) in complete growth media, while leaving some wells in complete growth media as controls of how the cells normally grow under normal conditions. Put the cells in incubator and let the assay go for 72hrs.

Day 5- Add 15ul/well of MTT reagent, let cells inc. for 4hrs., then add 100ul of stop solution, let cells inc. for an additional 1hr., then read the plate on a multilabel counter (Victor2, PerkinElmer Life Sciences Inc., Boston). The MTT protocol will give you two readings, one at a 650 wavelength (background) and one at a 572 wavelength. Subtract

the 650 reading from the 572 reading to get your actual output. These numbers are averaged and converted to a % inhibition value.

Results:

-Retnoic Acid gave a 53% inhibition of growth (positive control)

-IL-20 gave a maximal 20% inhibition of growth

WHAT IS CLAIMED IS:

1. A method for inhibiting the growth and or proliferation of cervical cancer cells comprising bringing Interleukin-20 (IL-20) into contact with the cervical cancer cells.

2. The method of claim 1 wherein the cervical cancer cells are treated with radiation in conjunction with IL-20.

3. The method of claim 1 wherein the cervical cancer cells are treated with one or more additional chemotherapeutic agents in conjunction with IL-20.

4. The method of claim 3 wherein the chemotherapeutic agent is selected from the group consisting of bleomycin, chlorambucil, epirubicin, 5-fluorouracil, ifosfamide, mitomycin, methotrexate, vincristine, cisplatin and vinblastine.

5. A method for treating a female mammal afflicted with cervical cancer comprising administering to said female mammal IL-20.

6. The method of claim 5 wherein the IL-20 is administered in conjunction with radiation.

7. The method of claim 5 wherein the IL-20 is administered in conjunction with a chemotherapeutic agent.

8. The method of claim 7 wherein the chemotherapeutic agent is selected from the group consisting of bleomycin, chlorambucil, epirubicin, 5-fluorouracil, ifosfamide, mitomycin, methotrexate, vincristine, cisplatin and vinblastine.

9. A method for inhibiting the proliferation or growth of human papillomavirus (HPV) comprising bringing IL-20 into contact with cells infected with HPV.

10. The method of claim 9 wherein the IL-20 is injected into a genital wart infected with HPV.

11. The method of claim 9 wherein the IL-20 is administered in conjunction with the consisting of interferon alpha, interferon beta, podophyllotoxin, podophyllin and 5-fluorouracil, trichloroacetic acid, and imiquimod.

12. The method of claim 9 wherein the IL-20 is administered in conjunction with electrocauterization, laser, cryotherapy, or surgical excision of the cells infected with HPV.

13. A method for treating an individual infected with HPV comprising administering to said individual a therapeutically effective amount of IL-20.

14. The method of claim 13 wherein said individual has genital warts or lesions infected with HPV and the IL20 is injected into the lesions or genital warts infected.

15. The method of claim 14 wherein said the IL-20 is injected into said warts in conjunction with electrocauterization, laser, cryotherapy, or surgical excision of the genital warts or lesions infected with HPV.

16. The method of claim 14 wherein the IL-20 is administered in conjunction with the consisting of interferon alpha, interferon beta, podophyllotoxin, podophyllin and 5-fluorouracil, trichloroacetic acid, and imiquimod.

17. The use of IL-20 for the production of a medicament for the treatment of cervical cancer.

18. The use of IL-20 for the production of a medicament for the treatment of human papilloma virus infection.

SEQUENCE LISTING

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            20                  25                  30
Asp Gly Asn Ile Asp Ile Arg Ile Leu Arg Arg Thr Glu Ser Leu Gln
        35                  40                  45
Asp Thr Lys Pro Ala Asn Arg Cys Cys Leu Leu Arg His Leu Leu Arg
    50                  55                  60
Leu Tyr Leu Asp Arg Val Phe Lys Asn Tyr Gln Thr Pro Asp His Tyr
65                  70                  75                  80
Thr Leu Arg Lys Ile Ser Ser Leu Ala Asn Ser Phe Leu Thr Ile Lys
                85                  90                  95
Lys Asp Leu Arg Leu Cys His Ala His Met Thr Cys His Cys Gly Glu
            100                 105                 110
Glu Ala Met Lys Lys Tyr Ser Gln Ile Leu Ser His Phe Glu Lys Leu
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            20                  25                  30
Asp Gly Asn Ile Asp Ile Arg Ile Leu Arg Arg Thr Glu Ser Leu Gln
        35                  40                  45
Asp Thr Lys Pro Ala Asn Arg Cys Cys Leu Leu Arg His Leu Leu Arg
    50                  55                  60
Leu Tyr Leu Asp Arg Val Phe Lys Asn Tyr Gln Thr Pro Asp His Tyr
65                  70                  75                  80
Thr Leu Arg Lys Ile Ser Ser Leu Ala Asn Ser Phe Leu Thr Ile Lys
                85                  90                  95
Lys Asp Leu Arg Leu Cys Leu Glu Pro Gln Ala Ala Val Val Lys Ala
            100                 105                 110
Leu Gly Glu Leu Asp Ile Leu Leu Gln Trp Met Glu Glu Thr Glu
        115                 120                 125
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Met Lys Gly Phe Gly Leu Ala Phe Gly Leu Phe Ser Ala
1 5 10

gtg ggt ttt ctt ctc tgg act cct tta act ggg ctc aag acc ctc cat 157
Val Gly Phe Leu Leu Trp Thr Pro Leu Thr Gly Leu Lys Thr Leu His
15 20 25

ttg gga agc tgt gtg att act gca aac cta cag gca ata caa aag gaa 205
Leu Gly Ser Cys Val Ile Thr Ala Asn Leu Gln Ala Ile Gln Lys Glu
30 35 40 45

ttt tct gag att cgg gat agt gtg caa gct gaa gat aca aat att gac 253
Phe Ser Glu Ile Arg Asp Ser Val Gln Ala Glu Asp Thr Asn Ile Asp
50 55 60

atc aga att tta agg acg act gag tct ttg aaa gac ata aag tct ttg 301
Ile Arg Ile Leu Arg Thr Thr Glu Ser Leu Lys Asp Ile Lys Ser Leu
65 70 75

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gat agg tgc tgc ttc ctt cgt cat cta gtg aga ttc tat ctg gac agg      349
Asp Arg Cys Cys Phe Leu Arg His Leu Val Arg Phe Tyr Leu Asp Arg
         80                  85                  90

gta ttc aaa gtc tac cag acc cct gac cac cat acc ctg aga aag atc      397
Val Phe Lys Val Tyr Gln Thr Pro Asp His His Thr Leu Arg Lys Ile
     95                 100                 105

agc agc ctc gcc aac tcc ttt ctt atc atc aag aag gac ctc tca gtc      445
Ser Ser Leu Ala Asn Ser Phe Leu Ile Ile Lys Lys Asp Leu Ser Val
110                 115                 120                 125

tgt cat tct cac atg gca tgt cat tgt ggg gaa gaa gca atg gag aaa      493
Cys His Ser His Met Ala Cys His Cys Gly Glu Glu Ala Met Glu Lys
                130                 135                 140

tac aac caa att ctg agt cac ttc ata gag ttg gaa ctt cag gca gcg      541
Tyr Asn Gln Ile Leu Ser His Phe Ile Glu Leu Glu Leu Gln Ala Ala
            145                 150                 155

gtg gta aag gct ttg gga gaa cta ggc att ctt ctg aga tgg atg gag      589
Val Val Lys Ala Leu Gly Glu Leu Gly Ile Leu Leu Arg Trp Met Glu
        160                 165                 170

gag atg cta tagatgaaag tggagaggct gctgagaaca ctcctgtcca             638
Glu Met Leu
    175

agaatctcag acctcagcac catgaagaca tggccccagg tgctggcatt tctactcaag    698
agttccagtc ctcagcacca cgaagatggc ctcaaaccac cacccctttg tgatataact    758
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<400> 19

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Cys Val Ile Thr Ala Asn Leu Gln Ala Ile Gln Lys Glu Phe Ser Glu
        35                  40                  45
Ile Arg Asp Ser Val Gln Ala Glu Asp Thr Asn Ile Asp Ile Arg Ile
    50                  55                  60
Leu Arg Thr Thr Glu Ser Leu Lys Asp Ile Lys Ser Leu Asp Arg Cys
65                  70                  75                  80
Cys Phe Leu Arg His Leu Val Arg Phe Tyr Leu Asp Arg Val Phe Lys
                85                  90                  95
Val Tyr Gln Thr Pro Asp His His Thr Leu Arg Lys Ile Ser Ser Leu
            100                 105                 110
Ala Asn Ser Phe Leu Ile Ile Lys Lys Asp Leu Ser Val Cys His Ser
        115                 120                 125
His Met Ala Cys His Cys Gly Glu Glu Ala Met Glu Lys Tyr Asn Gln
    130                 135                 140
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165 170 175

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<212> PRT
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35 40 45
Asp Ile Lys Ser Leu Asp Arg Cys Cys Phe Leu Arg His Leu Val Arg
50 55 60
Phe Tyr Leu Asp Arg Val Phe Lys Val Tyr Gln Thr Pro Asp His His
65 70 75 80
Thr Leu Arg Lys Ile Ser Ser Leu Ala Asn Ser Phe Leu Ile Ile Lys
85 90 95
Lys Asp Leu Ser Val Cys His Ser His Met Ala Cys His Cys Gly Glu
100 105 110
Glu Ala Met Glu Lys Tyr Asn Gln Ile Leu Ser His Phe Ile Glu Leu
115 120 125
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<210> 25
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Cys Val Ile Thr Ala Asn Leu Gln Ala Ile Gln Lys Glu Phe Ser Glu
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Leu Arg Thr Thr Glu Ser Leu Lys Asp Ile Lys Ser Leu Asp Arg Cys
35 40 45
Cys Phe Leu Arg His Leu Val Arg Phe Tyr Leu Asp Arg Val Phe Lys
50 55 60
Val Tyr Gln Thr Pro Asp His His Thr Leu Arg Lys Ile Ser Ser Leu
65 70 75 80
Ala Asn Ser Phe Leu Ile Ile Lys Lys Asp Leu Ser Val Cys His Ser
85 90 95
His Met Ala Cys His Cys Gly Glu Glu Ala Met Glu Lys Tyr Asn Gln
100 105 110
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<210> 26
<211> 144
<212> PRT
<213> Homo sapiens

<400> 26
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20 25 30
Leu Arg Arg Thr Glu Ser Leu Gln Asp Thr Lys Pro Ala Asn Arg Cys
35 40 45
Cys Leu Leu Arg His Leu Leu Arg Leu Tyr Leu Asp Arg Val Phe Lys
50 55 60
Asn Tyr Gln Thr Pro Asp His Tyr Thr Leu Arg Lys Ile Ser Ser Leu
65 70 75 80
Ala Asn Ser Phe Leu Thr Ile Lys Lys Asp Leu Arg Leu Cys His Ala
85 90 95
His Met Thr Cys His Cys Gly Glu Glu Ala Met Lys Lys Tyr Ser Gln
100 105 110
Ile Leu Ser His Phe Glu Lys Leu Glu Pro Gln Ala Ala Val Val Lys

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Ala Leu Gly Glu Leu Asp Ile Leu Leu Gln Trp Met Glu Glu Thr Glu
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<400> 27

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            20                  25                  30
Arg Thr Glu Ser Leu Gln Asp Thr Lys Pro Ala Asn Arg Cys Cys Leu
        35                  40                  45
Leu Arg His Leu Leu Arg Leu Tyr Leu Asp Arg Val Phe Lys Asn Tyr
    50                  55                  60
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35 40 45
Met Lys Lys Tyr Ser Gln Ile Leu Ser His Phe Glu Lys Leu Glu Pro
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Met Lys Gly Phe Gly Leu Ala Phe Gly Leu Phe Ser Ala
1 5 10

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ttg gga agc tgt gtg att act gca aac cta cag gca ata caa aag gaa      205
Leu Gly Ser Cys Val Ile Thr Ala Asn Leu Gln Ala Ile Gln Lys Glu
 30                  35                  40                  45

ttt tct gag att cgg gat agt gtg tct ttg gat agg tgc tgc ttc ctt      253
Phe Ser Glu Ile Arg Asp Ser Val Ser Leu Asp Arg Cys Cys Phe Leu
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cgt cat cta gtg aga ttc tat ctg gac agg gta ttc aaa gtc tac cag      301
Arg His Leu Val Arg Phe Tyr Leu Asp Arg Val Phe Lys Val Tyr Gln
             65                  70                  75

acc cct gac cac cat acc ctg aga aag atc agc agc ctc gcc aac tcc      349
Thr Pro Asp His His Thr Leu Arg Lys Ile Ser Ser Leu Ala Asn Ser
         80                  85                  90

ttt ctt atc atc aag aag gac ctc tca gtc tgt cat tct cac atg gca      397
Phe Leu Ile Ile Lys Lys Asp Leu Ser Val Cys His Ser His Met Ala
     95                  100                 105

tgt cat tgt ggg gaa gaa gca atg gag aaa tac aac caa att ctg agt      445
Cys His Cys Gly Glu Glu Ala Met Glu Lys Tyr Asn Gln Ile Leu Ser
110                 115                 120                 125

cac ttc ata gag ttg gaa ctt cag gca gcg gtg gta aag gct ttg gga      493
His Phe Ile Glu Leu Glu Leu Gln Ala Ala Val Val Lys Ala Leu Gly
                130                 135                 140

gaa cta ggc att ctt ctg aga tgg atg gag gag atg cta tagatgaaag      542
Glu Leu Gly Ile Leu Leu Arg Trp Met Glu Glu Met Leu
            145                 150

tggataggct gctgagaaca ctcctgtcca agaatctcag acctcagcac catgaagaca    602
tggccccagg tgctggcatt tctactcaag agttccagtc ctcagcacca cgaagatggc    662
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<400> 34

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            20                  25                  30
Cys Val Ile Thr Ala Asn Leu Gln Ala Ile Gln Lys Glu Phe Ser Glu
        35                  40                  45
Ile Arg Asp Ser Val Ser Leu Asp Arg Cys Cys Phe Leu Arg His Leu
    50                  55                  60
Val Arg Phe Tyr Leu Asp Arg Val Phe Lys Val Tyr Gln Thr Pro Asp
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65 70 75 80
His His Thr Leu Arg Lys Ile Ser Ser Leu Ala Asn Ser Phe Leu Ile
85 90 95
Ile Lys Lys Asp Leu Ser Val Cys His Ser His Met Ala Cys His Cys
100 105 110
Gly Glu Glu Ala Met Glu Lys Tyr Asn Gln Ile Leu Ser His Phe Ile
115 120 125
Glu Leu Glu Leu Gln Ala Ala Val Val Lys Ala Leu Gly Glu Leu Gly
130 135 140
Ile Leu Leu Arg Trp Met Glu Glu Met Leu
145 150

<210> 35
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<213> Mus musculus

<400> 35
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35 40 45
Phe Lys Val Tyr Gln Thr Pro Asp His His Thr Leu Arg Lys Ile Ser
50 55 60
Ser Leu Ala Asn Ser Phe Leu Ile Ile Lys Lys Asp Leu Ser Val Cys
65 70 75 80
His Ser His Met Ala Cys His Cys Gly Glu Glu Ala Met Glu Lys Tyr
85 90 95
Asn Gln Ile Leu Ser His Phe Ile Glu Leu Glu Leu Gln Ala Ala Val
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<210> 43
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<400> 43
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40309

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00, 39/00, 45/00
US CL : 424/85.1,198.1; 514/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/85.1,198.1; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/03982 A1 (HUMAN GENOME SCIENCE, INC.) 28 January 1999 (28.01.1999), see entire document.	1-18
A	US 6,486,301 B1 (EBNER et al) 26 November 2002 (26.11.2002), see entire document.	1-18
A	BLUMBERG et al. Interleukin 20: Discovery, Receptor Identification, and Role in Epidermal Function. Cell. 12 January 2001, Vol. 104, No. 1, pages 9-19, see entire document.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
02 April 2003 (02.04.2003)

Date of mailing of the international search report
22 APR 2003

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INTERNATIONAL SEARCH REPORT

PCT/US02/40309

Continuation of B. FIELDS SEARCHED Item 3:
STN DATABASE, MEDLINE, CANCERLIT, BIOSIS, CONFSCI, CAPLUS, EMBASE, SCISEARCH, USPATFULL, PCTFULL